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10/714,580	11/14/2003	Paul Wentworth	TSRI 784.5	1792

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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,580	WENTWORTH ET AL.	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-42,44,45 and 54-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-42,44,45 and 54-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 21, 2009 has been entered.

Claim Status

2. Claims 1-39, 43 and 46-53 are cancelled. Claims 40-42, 44-45 and 54-58 are under consideration in this office action.

Withdrawal of Rejections

3. The following rejections have been withdrawn in view of applicants' amendments and arguments:

a) The rejection of claims 48-51 under 35 U.S.C. 102(b) as being anticipated by Devanathan et al;

b) The rejection of claims 48-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Wentworth et al., in light of the Scripps Press Release of November 14, 2002; and

c) The rejection of claims 48-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Berthiaume et al.

Response to Arguments

4. Applicant's arguments filed April 29, 2009 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The new matter rejection of claims 40-42, 44 and 45 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained.

The rejection was on the grounds that neither the specification nor originally presented claims provides support for a method of generating a reactive oxygen species to inhibit the growth of a bacterium comprising contacting the bacterium with (i) an antibody or antibody fragment that can bind to the bacterium and (ii) a source of singlet oxygen wherein the source of singlet oxygen is not conjugated to the antibody or another molecule.

Applicants point to page 78, lines 1-4; page 83, lines 11-18; and page 93, lines 17-24 for support for the amendment. All of the sections recite that hematoporphyrin and antibody were added together. There is no teaching the source of the singlet oxygen is not conjugated to any other molecule; rather this is only a teaching that the source of the singlet oxygen is not conjugated to the antibody.

Applicant's arguments filed September 2, 2009 and April 21, 2009 have been fully considered but they are not persuasive. Applicant has argued that MPEP 2173.05(i) indicates that a negative limitation does not render a claim unclear. This argument pertains to a 112, 2nd issue, which is not the basis of rejection. Applicant should note that MPEP 2173.05(i) indicates (3rd para.) that "Any negative limitation or exclusionary proviso must have basis in the original disclosure" and that "the mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement." The most relevant case law cited therein is *Ex parte Grasselli* 231 USPQ 393.

Applicants assert that written description does not require verbatim and literal support and that claim limitations can be supported by implicit or inherent disclosures. However it is the position of the Office that the mere absence of a positive recitation i.e. of another molecule, to which the source of singlet oxygen could be conjugated is not a basis for an exclusion. See MPEP 2173.05(i). Applicant has not pointed to support, either implicitly or inherently of the conjugate not being conjugated to any molecule.

Applicants point to page 25, reciting that the sensitizer is not conjugated to antibody. Again, Applicant has not pointed to any place in the specification where the sensitizer is not conjugated to any molecule at all. It appears that applicants are asserting that the sensitizer not being conjugated to an antibody and not being conjugated to any other molecule are equivalent. However this is clearly not so; the absence of a positive recitation drawn to the sensitizer not being conjugated to an antibody is not basis for the exclusion of "any other molecules".

If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Therefore the Office has clearly set forth for Applicant the reasons for this rejection.

Applicant did not point to support in the specification for the instantly claimed method with respect to the recitation "or another molecule". Since the only disclosure teachings about the source of singlet oxygen being "conjugated" to anything were in the context of its being "conjugated to the antibody" (e.g. page 78, lines 1-4; page 83, lines 11-18; and page 93, lines 17-24) it constitutes new matter for applicant to recite that the source of singlet oxygen being "is not conjugated" to "another molecule". The mere

absence of a positive recitation (i.e. of another molecule, to which the source of singlet oxygen could be conjugated) is not a basis for an exclusion. See MPEP 2173.05(i).

Applicants point to a quotation in *In re Wakefield*, 422 F.2d 897, 899, 904, 164 USPQ 636, 638, 641 (CCPA 1970) concerning whether the claim is indefinite. However Applicant is reminded that the instant rejection is not a 112 2nd paragraph rejection; instead the issue is that the negative limitation does not have basis in the original disclosure.

Therefore applicants' arguments are not persuasive and the rejection is maintained contrary to applicants' arguments.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 40, 45, 54 and 58 are rejected under 35 U.S.C. 102(b) as being anticipated by De Baetselier (4,737,455, cited on PTO-892) in light of Wentworth Jr, (Science, 296, 2247, 2002).

Claim 40 is drawn to a method of generating ozone to inhibit the growth of a bacterium comprising contacting the bacterium with (I) an antibody that can bind to the

bacterium and (ii) a source of singlet oxygen ($^1O_2$) to thereby generate ozone to inhibit the growth of the bacterium, wherein the source of singlet oxygen is not conjugated to the antibody or another molecule. Claim 54 is drawn to a method of generating ozone to inhibit the growth of a bacterium comprising contacting the bacterium with (i) an antibody that can bind to the bacterium and (ii) a source of singlet oxygen ($^1O_2$) to thereby generate ozone to inhibit the growth of the bacterium, wherein the source of singlet oxygen is not conjugated to the antibody and the source of singlet oxygen would not, on its own, inhibit the growth of the bacterium when exposed to light. Claims 45 and 58 are drawn to the antibody being a Fab, Fab', F(ab')2, Fv or sFv fragment.

De Baetselier shows assays for an antibody, in which antibody, is combined with a sample and with a phagocytic cell line. If an antigen-antibody complex is formed, it will be opsonized by the phagocytic cells, and chemiluminescent light will be emitted (col. 7, line 61-col. 8, line 33, Examples 2 and 7Q). The chemiluminescent response of the phagocytes is linked to the formation of "unstable oxygen compounds" (col. 1, lines 17-23). Wentworth Jr provide evidence that such "unstable oxygen compounds" arise from "oxidative burst" of phagocytes, in which 0_2- and H_20_2 and $^1O_2$ are formed (Wentworth Jr at p 2249, col. 1). Wentworth Jr provides evidence that all antibodies inherently have a reactive center that is capable of generating 0_2- and H_20_2 and $^1O_2$ (Wentworth Jr at p 2249, col. 1). Since all antibodies have the inherent capability of generating 0_2- and H_20_2 and from the $^1O_2$ formed in the respiratory burst of phagocytes, and since the antigen-antibody complexes are opsonized on the surfaces of the cells that are the source of $^1O_2$ formed, it is properly considered that the antibodies used in or detected in

the assays of De Baetselier would have generated 0_2- and/or H_20_2 from the $^10_2$ produced by the phagocytic cells of De Baetselier. The phagocytes used in the assays of De Baetselier serve as a "source of singlet oxygen". When an antigen-antibody complex is formed in the assays of De Baetselier, the antigen is "contacted" with the antibody. It is noted that De Baetselier teach specific antibodies against stimulators such as bacteria and in particular *micrococci* or *Streptococci* (col. 8, lines 20-23, col. 9, lines 1-5; and Example 2).

Therefore De Baetselier teaches the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 40-42, 45 and 54-56 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rakestraw et al., (Biotechnol. Prog. 1992. Vol. 8:30-39) in view of Berthiaume et al (Biotechnology Vol. 12 July 1994:703-706).

Claim 40 is drawn to a method of generating ozone to inhibit the growth of a bacterium comprising contacting the bacterium with (I) an antibody that can bind to the bacterium and (ii) a source of singlet oxygen ($^10_2$) to thereby generate ozone to inhibit the growth of the bacterium, wherein the source of singlet oxygen is not conjugated to

the antibody or another molecule. Claim 54 is drawn to a method of generating ozone to inhibit the growth of a bacterium comprising contacting the bacterium with (i) an antibody that can bind to the bacterium and (ii) a source of singlet oxygen ($^1O_2$) to thereby generate ozone to inhibit the growth of the bacterium, wherein the source of singlet oxygen is not conjugated to the antibody and the source of singlet oxygen would not, on its own, inhibit the growth of the bacterium when exposed to light.

Claims 41 and 55 are drawn to the source of singlet oxygen being a sensitizer molecule. Claims 42 and 56 are drawn to the sensitizer molecule being chlorin. Claims 45 and 58 are drawn to the antibody being a Fab, Fab', F(ab')2, Fv or sFv fragment.

Rakestraw et al., teach photophysical properties of Sn(IV) chlorine e6 (SnCe6). Rakestraw et al., teach targeted photolysis which comprises melanoma cells, an anti-melanoma monoclonal antibody and the production of the potentially lethal excited species generated by the photosensitizer and molecular oxygen (page 30, col. 2). Rakestraw et al., show examples of SnCe6 + Monoclonal Antibody wherein the source of the singlet oxygen is not conjugated to the antibody or any other molecules, such that photolysis occurred (Table III). Rakestraw et al., teach cosolutions of unconjugated SnCe6 with monoclonal antibody being examined along with the production of singlet oxygen (page 34, col.2). However Rakestraw et al., teach antibodies binding to cancerous cells and not antibodies binding bacteria.

Berthiaume et al., the use of antibody targeted photolysis treatments of cancerous tumors is well known in the art (page 703, col. 1). Berthiaume et al., teach applying antibodies targeting microbial infections wherein the antibody targets *P.*

aeruginosa is well known in the art also (page 703, col.1). Bertiaume et al, teach bacterial killing *in vitro* using tin (IV) chlorine e6 as the photosensitizer has been shown to the highly efficient and likely mediated via the production of singlet oxygen and other short lived species (page 703, col. 1). Berthiaume et al., teach transport studies of antibody fragments have shown improved and rapid infiltration of the selected target sites (page 705).

Therefore, it would have been prima facie obvious at the time of applicants' invention to apply Berthiaume et al., antibodies that can bind bacterium to Rakestraw et al., methods of generating ozone to inhibit the growth of a bacterium et al., in order to provide antibodies which allow for selected target sites to be bound. One of ordinary skill in the art would have a reasonable expectation of success by incorporating alternative yet equivalent antibodies into the method, since the art teaches that photosensitizers such as SnCe6 and any antibodies will produce a lethal excited species that inhibits the target. Finally all the claimed elements were known in the prior art and one skilled in the art could have combined the elements including exchanging the antibodies within the known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 40-42, 44-45 and 54-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wentworth et al., in light of the Scripps Press Release of November 14, 2002 in view of Berthiaume et al (Biotechnology Vol. 12 July 1994:703-706).

Claim 40 is drawn to a method of generating ozone to inhibit the growth of a bacterium comprising contacting the bacterium with (I) an antibody that can bind to the bacterium and (ii) a source of singlet oxygen (102) to thereby generate ozone to inhibit the growth of the bacterium, wherein the source of singlet oxygen is not conjugated to the antibody or another molecule. Claim 54 is drawn to a method of generating ozone to inhibit the growth of a bacterium comprising contacting the bacterium with (i) an antibody that can bind to the bacterium and (ii) a source of singlet oxygen (102) to thereby generate ozone to inhibit the growth of the bacterium, wherein the source of singlet oxygen is not conjugated to the antibody and the source of singlet oxygen would not, on its own, inhibit the growth of the bacterium when exposed to light.

Claims 41 and 55 are drawn to the source of singlet oxygen being a sensitizer molecule. Claims 42 and 56 are drawn to the sensitizer molecule being hematoporphyin. Claims 44 and 57 are drawn to the antibody being human or humanized. Claims 45 and 58 are drawn to the antibody being a Fab, Fab', F(ab')2, Fv or sFv fragment.

Wentworth et al., (PNAS, 2000) teach antibodies have the intrinsic capacity to destroy antigens. Antibodies are remarkably adaptable molecules and are known for targeting and effector functions used by vertebrates a defense against foreign invaders (page 10,930). Antibodies are also capable of simply binding and more complex chemical reactions (page 10,930). Antibodies have the capacity to convert molecular oxygen into hydrogen peroxide, thereby effectively linking recognition and killing events (page 10,930). Wentworth et al., disclosed this capability with whole antibodies and $F(ab')_2$ fragments (see the materials and methods section). The sensitization and quenching assays teach a solution of horse IgG antibody and sensitizer molecule, hematopophyrin were placed in proximity to a strip of light and the concentration of hydrogen peroxide produced was determined (page 10,930). Wentworth et al., teach that superoxide anion radicals are the direct precursor of hydrogen peroxide and the toxic derivatives it spawns, such as hydroxyl radials (HO*). Thus Wentworth et al., teach that the reactive oxygen species generated is a superoxide radical, hydroxyl radical or hydrogen peroxide. Wentworth et al., teach irradiation of antibodies with visible light in the presence of a photosensitizer of $^3O_2$ hematoporphyrin leads to hydrogen peroxide formation (Figure 5A). Figure 5 shows hematoporphyrin in the presence of an antibody IgG.

It is noted that the art is silent with respect to the generation of an ozone as a reactive oxygen species. It is noted that the Scripps Press Release inherently teaches the production of ozone by antibodies during bacterial killing has played an hitherto unknown role in immune protection (Scripps Press Release). The ozone is part of a

previously unrecognized killing mechanism that enhances the defensive role of antibodies by allowing them to subject pathogens to hydrogen peroxide and participate directly in their killing. Antibodies produce the chemical oxidant hydrogen peroxide which is lethal to bacterial cells because it pokes holes in their cell walls, bursting the cells and killing them. The antibodies reduce singlet oxygen and produce ozone as a side product. The authors state that all antibodies have the ability to do this. Therefore the generation of hydrogen peroxide and ozone as a side product, are inherent abilities that antibodies have. Thus, the Scripps Press Release teaches that inherently, antibodies will generate ozone as a reactive species which will inhibit the growth of a bacterial microbe. However, Wentworth does not teach that the antibody can bind to the bacterium.

Berthiaume et al., has been discussed above as teaching antibodies targeting microbial infections wherein the antibody targets *P. aeruginosa* is well known in the art also (page 703, col.1). Berthiaume et al., teach transport studies of antibody fragments have shown improved and rapid infiltration of the selected target sites (page 705).

Therefore, it would have been prima facie obvious at the time of applicants' invention to apply Berthiaume et al., antibodies that can bind bacterium to Wentworth methods of generating ozone to inhibit the growth of a bacterium et al., in order to provide antibodies which allow for selected target sites to be bound. One of ordinary skill in the art would have a reasonable expectation of success by incorporating well known alternative yet equivalent antibodies into the method, since the art teaches that photosensitizers and any antibodies will produce a lethal excited species that inhibits

the target. Finally all the claimed elements were known in the prior art and one skilled in the art could have combined the elements including exchanging the antibodies within the known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Conclusion

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/
Primary Examiner, Art Unit 1645